## REMARKS

Upon entry of the above claim amendments, claims 3-9 are currently pending in the present application. Claim 9 is new, while claims 1 and 2 have been cancelled without prejudice.

Claim 8 has been amended to more clearly define the subject matter of this invention. Support for the amendment can be found throughout Applicants' specification, for example, lines 4-5 and 21-23 of page 5 of the application as originally filed.

Support for claim 9 can be found at pages 34 through 36 of Applicants' specification.

No new matter has been introduced.

Applicants respectfully reserve the right to pursue any non-elected, cancelled or otherwise unclaimed subject matter in one or more continuation, continuation-in-part, or divisional applications. Rejections of cancelled claims are considered moot and will not be addressed herein.

Reconsideration and withdrawal of the rejections of the present application in view of the remarks herewith, is respectfully requested, as the application is in condition for allowance.

## CLAIM REJECTIONS – 35 U.S.C. § 103(a)

a) Rejections over Samour in view of Piasecki and Cooper

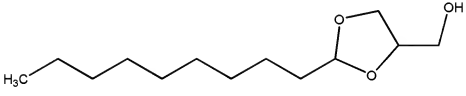
Claims 1-5 and 8 have been rejected as allegedly being obvious over U.S. patent No. 4,861,764 to Samour *et al.* (hereinafter "Samour") in view of Piasecki *et al.* (Abstract of PL 175837; hereinafter "Piasecki") and U.S. patent No. 4,557,934 to Cooper *et al.* (hereinafter "Cooper"). Applicants respectfully traverse.

Nonetheless, without conceding to the Examiner's allegation and solely for the purpose to expedite the prosecution of this application, claims 1 and 2 have been cancelled in this paper. Applicants further submit that the present invention is non-obvious over Samour in view of Piasecki and Cooper.

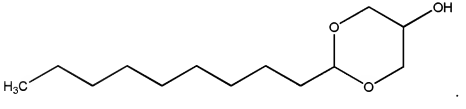
To properly determine a prima facie case of obviousness, the Examiner "must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art'

when the invention was unknown and just before it was made." M.P.E.P § 2142. Three criteria may be helpful in determining whether claimed subject mater is obvious under 103(a): first, if there is some suggestion or motivation to modify or combine the cited references; second, if there is a reasonable expectation of success; and third, if the prior art references teach or suggest all the claim limitations. *KSR Int'l Co. v. Teleflex, Inc.* No 04-1350 (U.S. Apr. 30, 2007). With regard to the first criterion, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills,* 916 F.3d 690 (Fed. Cir. 1990). "Knowledge in the prior art of every element of a patent claim ... is not of itself sufficient to render claim obvious." *Graham v. John Deere Co.,* 383 U.S. 1, 17-18 (1966); *Teleflex, Inc. v. Ficosa N. Am. Corp.,* 299 F.3d 1313, 1333-34 (Fed. Cir. 2002). The issue is whether there is an apparent reason to combine the known elements in the fashion claimed by the patent at issue. *KSR Int'l Co. v. Teleflex, Inc.*

The present invention is directed to a method to improve permeation of a pharmaceutically active substance across a cell barrier comprising co-administering the pharmaceutically active substance with a combination of two materials, that is, compound 1:




and compound 2:

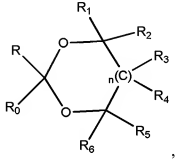



The present application also relates to a composition to improve permeation of a pharmaceutically active substance across a cell barrier, wherein the composition contains compound 1 and compound 2 (claim 8).

The instant claims further recite the method comprising co-administering compounds 1

and 2 in the ratio of about 9:1 (claim 4), or having an antibiotic or antiparasitic compound as the pharmaceutically active substance (claim 5).

In contrast, Samour is directed to a therapeutic composition suitable for transdermal administration of a physiologically active agent, wherein the therapeutic composition includes **a** penetration enhancer as defined in the following formula:



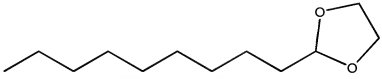

,

in which all the variables are defined therein.

Applicants respectfully submit that Samour does not teach or suggest either compound 1 or compound 2, let alone a method (or composition) of co-administering compounds 1 and 2 with a pharmaceutically active substance. Further, Applicants note that Samour does not even teach or suggest a method or composition wherein more than one permeation enhancer is used.

Nevertheless, the Examiner has asserted that compounds taught in Samour and compounds of the present application have similar structures, and that the Samour compounds and those of the present application would have the same properties and function (see, e.g., page 8 of the Action). In particular, the Examiner alleged that 2-n-nonyl-1,3-dioxolane (Example III) and 2-n-nonyl-1,3-dioxane (Example XIII) in Samour are structurally similar to compounds 1 and 2 of this invention, and that "the same properties and function" can be expected. Applicants respectfully disagree.

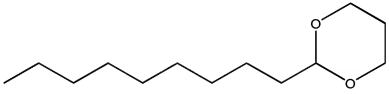
Applicants herein submit that Examples III and XIII are different type of compounds from compounds 1 and 2. To evidence the dissimilarity, the structures of 2-n-nonyl-1,3-dioxolane (Example III) and 2-n-nonyl-1,3-dioxane (Example XIII) are provided as follows:



2-n-nonyl-1,3-dioxolane (Example III)

,

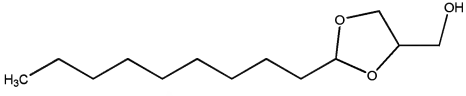
and



2-n-nonyl-1,3-dioxane (Example XIII)

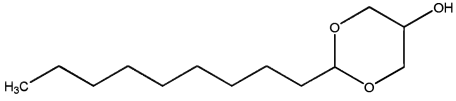
;

while compound 1 and compound 2 have the following chemical structures:



(2-nonyl-1,3-dioxolan-4-yl)methanol (Compound 1)

and



2-nonyl-1,3-dioxan-5-ol (Compound 2)

As evidenced by the above structures, Examples III and XIII are unsubstituted dioxolane/dioxane direvatives, while compound 1 is hydroxylmethyl-substituted dioxolane, and compound 2 is hydroxyl-substituted dioxane. Further, a skilled artisan would understand that compound 1 and compound 2 belong to the group of fatty alcohols, and that Examples III and XIII do not.

Applicants also submit that a person skilled in the art would expect that Examples III and XIII in Samour demonstrate different properties and functions from compounds 1 and 2. In particular, the two hydroxyl compounds (i.e., compounds 1 and 2) would be expected to have

some fundamentally distinct chemical properties, compared to the two Samour compounds. For example, the polarity of compound 1 or 2 would be higher than that of Example III or XIII respectively. Further, compound 1 or 2 would demonstrate a distinct amphiphilic nature, which would not be found in either Example III or Example XIII.

Furthermore, Applicants submit that there is no teaching or motivation provided by Samour to modify its compounds or delivery system to arrive at the present invention. Samour does not furnish any suggestion or motivation to a skilled artisan to modify Examples III and XIII by attaching any substituents to their ring structures, let alone the specific substituents (i.e., hydroxylmethyl and hydroxyl) as required by the present invention.

Further, Applicants note that only two hydroxyl compounds (i.e., Example XI and Example XII) are disclosed in Samour. These hydroxyl compounds are completely different in structures from compounds 1 and 2, as Examples XI and XII are unsaturated while compounds 1 and 2 are saturated. Furthermore, these hydroxyl compounds are clearly less favored by Samour, as evidenced by the fact that none of Samour's favored compounds (that is, Examples III, IV, V, VI, VIII, XIII, XIV, and XV) have hydroxyl substituents on its structure (*see* col. 9, lines 20-24, and lines 50-65 of Samour). As such, Samour clearly favors non-hydroxyl-substituted compounds over hydroxyl compounds (as directed in this invention) as penetration enhancers. Given these teachings or suggestions in Samour, a skilled artisan would conclude that Samour indeed teaches away from the instant invention.

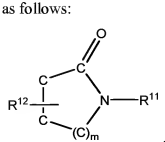
Additionally, Applicants submit that the present invention has unexpectedly achieved surprisingly effective permeation effects compared to the Samour permeation carriers. For example, Table 3 in Applicants' specification demonstrates that the presently claimed delivery systems significantly increased permeation of the medicament mebendazole through blood-brain barrier, which resulted in at least 16-fold improvement in reducing the worm infection at a more than 30-fold reduced mebendazole dose. As contrast, the best result offered by Samour was achieved through using Example III as the enhancer, in which only about 8-fold improvement was observed in percutaneous Indomethaci absorption at presumably the same drug dose (*see* col. 10 of Samour). Applicants note that the rest of Samour's test results show little or modest

permeation improvement. In view of Samour's disclosure, there is no reasonable expectation to a skilled artisan that the a combination of two hydroxyl compounds (e.g., compounds 1 and 2) could possibly achieve a dramatically increased permeation of a medicament as reported in the present application.

At least for the above reasons, the present invention is non-obvious over Samour. Applicants further submit that Piasecki and Cooper fail to cure the deficiencies of Samour.

While Piasecki mentions using compound 2 as a possible surfactant, Piasecki does not teach or suggest using compound 1 at all, let alone combining compounds 1 and 2 for a permeation system. Neither does Piasecki provide any motivation or suggestion to modify compound 2 to obtain compound 1. Furthermore, Piasecki does not mention at all any enhanced penetrating effect that compound 2 might possibly have, let alone co-administering compounds 1 and 2 for enhancing penetration effects, or formulating a composition containing compounds 1 and 2 to improve permeation. Indeed, a skilled artisan could conclude that Piasecki only teaches ways to make compound 2, and nothing more. Thus, Applicants submit that Piasecki fails to cure the deficiencies of Samour.

The addition of Cooper does not render the present invention obvious either, as Cooper also fails to cure the deficiencies in Samour and Piasecki. First, Cooper does not teach or suggest compound 1, let alone a combination of compound 1 and compound 2 for use as a permeation carrier. Second, contrary to the Examiner's assertion at page 7 of the Action, Applicants respectfully contend that Cooper does not provide a general preference for binary combinations. Instead, Cooper teaches only specific binary systems that combine Azone with a diol, and/or certain N-substituted-azacycloalkyl-2-ones. The general formula of N-substituted-azacycloalkyl-2-ones (including Azone) is shown as follows:




Clearly, N-substituted-azacycloalkyl-2-ones taught in Cooper are lactams, which belong to a

completely different class of compounds, compared to compound 1 or 2 of this invention.

Thus, in view of Cooper's teachings, a skilled artisan would conclude that Cooper does not offer a general preference on binary penetration systems (except only a few specific ones). Further, Applicants respectfully note that Cooper does not teach compound 2 (or even any compound with a similar structure) for a binary penetration delivery. Accordingly, a skilled artisan cannot possibly find in Cooper any suggestion/motivation for combining compound 2 with anything else, let alone a specific combination comprising compound 1 and compound 2 (as directed in this invention). Thus, Applicants contend that one skilled in the art would not be motivated by Cooper to modify the delivery system therein to reach the present invention.

In summary, Applicants respectfully submit that: first, the cited art (i.e., Samour, Piasecki and Cooper) fails to teach or disclose compound 1 as an enhancer; second, there is absolutely no suggestion or motivation provided by Samour, Piasecki, and/or Cooper for modifying their compounds or delivery systems to arrive at the presently claimed invention, which requires a co-administration of compound 1 and compound 2; third, there would have been no reasonable expectation of success in achieving the present invention in absence of such teaching or motivation as above-discussed; and finally, the present invention has unexpectedly achieved surprisingly dramatic permeation effects in light of the teachings in the cited art. Therefore, the present invention is indeed patentable over Samour in view of Piasecki and Cooper.

At least for the above reasons, reconsideration and withdrawal of the rejections of the instant application over Samour in light of Piasecki and Cooper is respectfully requested.

b) Rejections over Samour in view of Piasecki and Cooper, and further in view of Grasela

Claims 6 and 7 have been rejected as allegedly being obvious over Samour in view of Piasecki and Cooper and further in view of U.S. patent No. 5,837,289 to Grasela *et al.* (hereinafter "Grasela"). Applicants respectfully traverse.

These claims are directed to a method to improve permeation of a pharmaceutically active substance comprising co-administering compound 1 and compound 2. The instant claims

further recite that the antibiotic as the pharmaceutically active substance is fluoroquinolone (claim 6), or that the antiparasitic compound is mebendezole (claim 7).

The above remarks are applicable in comparing the present invention with the teachings of Samour, Piasecki and Cooper, as such that the method of this application is indeed patentable over Samour in view of Piasecki and Cooper.

Here, Applicants further submit that the addition of Grasela does not render the present invention obvious. Applicants note that Grasela fails to teach compound 1, let alone a method of co-administering compound 1 and compound 2 with the specific pharmaceutically active substances. Further, Grasela does not teach or suggest any penetrating enhancer that has a similar structure to that of compound 1 or compound 2. Additionally, Grasela does not provide any suggestion or motivation to a skilled artisan in achieving the instant invention. Indeed, Grasela adds nothing to the teachings in Samour, Piasecki and Cooper. Therefore, the instant claims are patentable over Samour in view of Piasecki and Cooper and further in view of Grasela.

At least for the above reasons, reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a) of claims 6 and 7 is respectfully requested.

## CONCLUSIONS

In view of the remarks made herein, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are respectfully requested. If the Examiner believes that a telephone conversation with Applicants' attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney. Also, please charge any required fee or credit any overpayment to Deposit Account No. 04-1105, under Order No. 81647 (303989).

Dated: April 7, 2009

Respectfully submitted,

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